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MODERN CONCEPTS OF CARDIOVASCULAR DISEASE

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Epidemiology and Cardiovascular Disease of Middle Age: Part II*†

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EPIDEMIOLOGY OF HEALTH

A general question may be asked. Do men who take regular exercise, smoke but little, and consume liberal quantities of polyunsaturated fat, have a different metabolism and a healthier cardiovascular system than their opposites? Do they develop less ischaemic heart disease (IHD)? And how does this relate to inherited susceptibilities? These are some of the questions we must try to answer. The present hope is that many environmental factors are involved and that modification of several, rather than a revolution in one, may give us a regimen for the preventive medicine of tomorrow.[5, 7, 32] Meanwhile, the challenge remains that in a population largely sedentary, smoking heavily, and richly fed, only a small minority suffer from IHD in middle age.

DETECTING THE SUSCEPTIBLES

Finding the causes of IHD should give us methods of prevention. The other approach to prevention is to define those who are particularly susceptible and then, perhaps by empirical methods, attempt individually to reduce their susceptibility. What has been learned about the causes would also be applied.

It is not so long since it was argued whether the hypercholesterolaemia of patients with IHD, particularly the younger men, antedated the clinical event or was produced by it. This is a typical question to be answered only by the long-term follow-up of large numbers of individuals.[12, 14] In figure 3, we observe that high blood cholesterol, like hypertension, and independently of it, is clearly predisposing[24] (Dawber, T. R., personal communication, 1960). This kind of fact is immediately useful as a means of identifying susceptibles: for example, about 20 per cent of men with high, or the tendency to high, blood pressure and blood

RISK OF CORONARY HEART DISEASE ACCORDING TO LEVEL OF SERUM CHOLESTEROL, FRAMINGHAM MEN 45-62, WITH VARIOUS LEVELS OF DIASTOLIC BLOOD PRESSURE

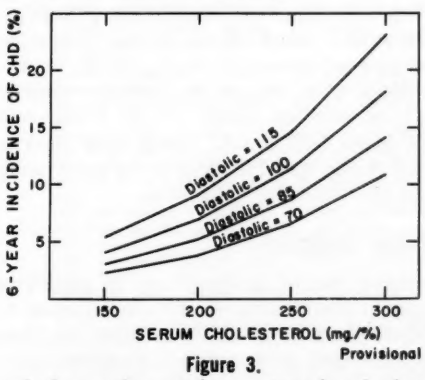

Figure 3.

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lipids are particularly vulnerable (they account for about 40 per cent of the incidence of IHD in the Framingham population; in Albany, the findings are by no means so clear-cut). With this kind of observation, there is a possibility of starting preventive treatment before IHD is manifest and, it could be, before tissue changes are irreversible. It can also be said on the basis of the Framingham study that, on the average, men with blood cholesterol of less than 200 mg. per cent are relatively immune to IHD; at any rate, they do not present a major public health problem. Unfortunately, there seem to be few such individuals; however, a crucial group has been identified here for study.[36]

Causes of Susceptibility

But we cannot escape the question: What are the causes of hypercholesterolaemia? Is it inheritance? Saturated fat? Other nutrients? Smoking? Physical inactivity? Emotion and psychosocial situations? All of these? And others? A little of the evidence on external factors has already been presented. Diet is today under the strongest suspicion, and the main hypothesis on the aetiology of IHD is dietary. Within the range of 80-200 Gm. of fat, apparently consumed by males in England, about half is saturated. Are the individual blood lipid levels affected by this diet? What is the diet of the men with less than 200 mg. per cent? A tentative investigation by our research unit in England so far has shown no association whatsoever in the individual, at current levels of consumption, between what is known of habitual calorie or fat intake and casual blood lipid levels. Much more work is needed on this question, both in the community and in the metabolic ward.

CORONARY DISEASES?

Another use of epidemiology of particular interest to the clinician is the identification of specific diseases, syndromes, or processes from undifferentiated clinical data. Thus, the analysis and classification of clinical material by its frequency in social and other groups may show that what is regarded as an entity cannot be so because its parts are differently distributed.[36] In this illustration, the author's intention is to be provocative. Consider coronary "atherosclerosis." In table 1, it was suggested that the recent history of coronary-mural atheroma and coronary-lumen occlusion were different. Furthermore, in figure 2 it seemed that mural atheroma was not particularly related to the physical activity of occupation (sections 3a and 3b), but that coronary occlusion was (3d). In the same necropsy survey, it was noted, for example in hypertensive disease, that an increase of occlusion occurred, as expected, with a gross increase of mural atheroma. But in deaths from peptic ulcer, there was an average amount of mural atheroma in the coronary arteries and yet a sharp increase in coronary occlusion was found; again a dissociation in behaviour. Another argument is more theoretical: it concerns the nature and the amount of the two processes in the population, as illustrated in table 2, and is even clearer at younger ages. Mural atheroma is exceedingly common. During middle age, at any rate, it is commoner to have a little of it than a moderate amount, and also more usual to have a moderate amount than a lot. With obstruction of the lumen, it seems to be different; only a minority have it at all. Of these, through some feedback, self-accelerating, all-or-none type of mechanism, a disproportionate fraction seems to have a great deal. (To complete the population picture, cases of IHD must be added in their proper proportion to those of table 2.)

Thus, the epidemiological evidence suggests that coronary "atherosclerosis" may in fact be two diseases or, perhaps, includes two distinct processes which are related but not the same. Much more than mural atheroma evidently is involved in coronary occlusion. Moreover, it is a common clinical observation at post-mortem that many individuals have gross mural atheroma without obstruction and, perhaps, even with dilatation. However, some with little atheroma suffer fatal occlusion. To my mind, the most reasonable interpretation of the work of Duguid and his school is that there are two types of lesion: (a) fatty, and (b) fibrinous. Both affect the walls, but it is the latter that produces the serious obstruction of the lumen. (Perhaps what has increased is fibrin disease.) The resolution of the century-long argument may be neither Virchow nor Rokitansky, but both. If so, the causes of atheroma and of occlusion cannot be just the same. The long laboratory-experimental history of production of atheroma and the near impossibility, until recently, of producing coronary thrombosis and occlusion, may be pointing the same way; although it is not yet clear whether recent successful laboratory manoeuvres are qualitatively, or only quantitatively, different from previous ones. And there is a new variable in the pos-

Figure 4. Exploring Essential Hypertension

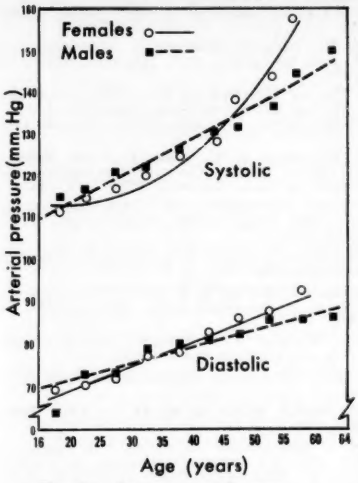

Fig. 4a. Increase with age.

Per cent of casual diastolic blood pressure >100mm.Hg		
Age	So. Wales	Jamaica
25-34	6.3	6.7
35-44	9.8	12
45-54	14	17
55-64	18	24
65-74	19	28

Fig. 4b. White and Negro men.

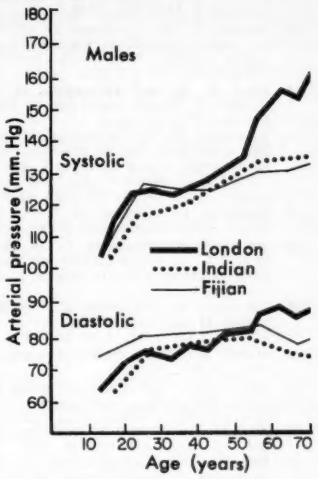

Fig. 4c. No rise middle age.

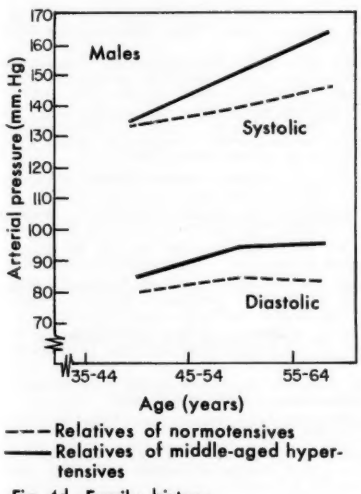

Fig. 4d. Family history.

Per cent of casual systolic blood pressure > 180mm.Hg		
Drivers	Stokers	Shunters
13	6.3	2.5

Fig. 4e. Occupation: 1,469 railwaymen aged 40-49.

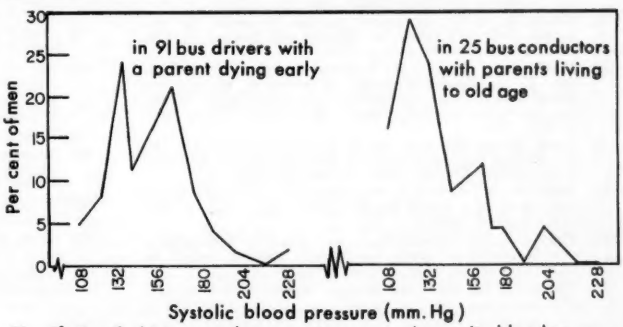

Fig. 4f. Family history and occupation: casual systolic blood pressure in men aged 50-60.

Obesity	Prevalence of hypertension	Incidence of hypertension	Incidence of hypertensive heart disease
None/slight	128	31	8
Moderate	229	38	13
Marked	368	54	16

Fig. 4g. Obesity: rates per 1,000 men, aged 50-59.

Per cent of casual pressure 140/90mm. Hg and over	
Low	1
Moderate	7
High	11

Fig. 4h. Salt intake (in the "High" group, overweight increases the prevalence).

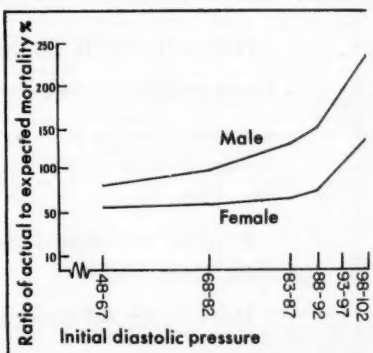

Fig. 4i. Sex: actuarial experience.

TABLE 7

Geographical Pathology: Aortic Atherosclerosis in Three Populations (Deaths from Accidents in Men)

Condition of Aorta	Ages 21-30			Ages 31-40		
	Bantu	New Orleans Negro	New Orleans White	Bantu	New Orleans Negro	New Orleans White
Average % surface involvement with:						
Fatty streaks	16	16	20	21	18	29
Fibrous plaques	<1	<1	<1	<1	3	12

Numbers so far collected are small.
(Strong, Wainwright, and McGill 1959.[51])

sibility of local arterial production of fatty lesions. Thus, the three methods of medical enquiry, each with its own resources and limitations, are being used to ask questions and provide information on this central issue. A further epidemiological step (returning to geographical pathology) would be to consider whether the two lesions in table 7, from Holman's School, represent early stages of what is being discussed.

EXPLORING ESSENTIAL HYPERTENSION

Finally, let us glance at a problem in an even earlier stage of investigation. Figure 4 represents some current attempts to clarify the great mystery of high blood pressure without evident cause, a disease predominantly of middle age or, at any rate, observed most clearly at that time. Such is our ignorance of the natural history of essential hypertension that even this innocuous statement should certainly be disputed. The author trusts that it is clear by now that epidemiology, by a study of the natural history of disease in the community–a study that necessarily includes every one, the sick and the majority who are not sick–may assist in clarifying such issues.

Some results from a survey in Scotland[4] are given in figure 4a: the figure shows the increase with age of systolic and diastolic blood pressures (male and female). It is a typical report, with its crossover (the menopause?) producing the higher figures among women from middle age already noted in table 3. The greater rise of systolic pressure is also expected and may be a simple statistical statement of rigidity in large vessels.

Figures 4b and 4c present contrasts from "geographical physiology." Figure 4b is from sample studies by Miall, who made the same observations in Southern Welshmen and Jamaican Negroes.[30] It has long been known that Negroes have higher blood pressure than whites.[41] But what inherited and acquired characteristics are involved is still largely unknown; the epidemiological lead has not been taken up by clinicians and laboratory workers. (Among the Jamaicans, manifest renal disease was uncommon.) A point to be mentioned here is the gross difference between the rates of high casual pressure found on ad hoc search and survey in South Wales and those of actual morbidity observed by general practitioners (table 3). This is a difference between per cent and per mille. The "plane" of diagnosis is surely only one of the factors involved, and the complex of hypertension/anxiety/atherosclerosis/cardiac hypertrophy (no chain of events implied) urgently requires sorting out in long-term follow-up studies.

Figure 4c shows that the rise of blood pressure during middle age is not universal or inevitable. The top line is from the population sample of G. W. Pickering and his group in London;[19] the Indians and Fijians are described in a recent study of Lovell and colleagues.[28]

Figure 4d proceeds to family studies and compares the experience during middle age of relatives of normotensive and of hypertensive subjects.[20, 48] The average increase among the former is less–scarcely any in diastolic pressure –the rise among the latter is "excessive," in Allbutt's phrase. Here again is an example of the wrong way of asking the right question: group averages of blood pressure are a poor substitute for the follow-up of levels in individuals to determine what happens in individuals. The study of the disease in families, with the clustering of cases that will be found, is an illustration of Paul's clinical epidemiology,[40] another meeting ground of the kind the author has been attempting to indicate for clinician and epidemiologist. It must be kept in mind that a great deal is shared in the family: genes and character development, patterns of behaviour, and the physical environment. Present family studies can scarcely be called population genetics, but here again is a probe of the future.

Figure 4e is an interesting occupational study from Czechoslovakia[21] (Kotačka, L., personal communication). East European research in hypertension emphasises the nervous strain involved in the job (stationmasters also had a high

rate), although this is difficult to dissociate from the physical activity, as illustrated previously for categories of workers instead of particular jobs in the frequency of hypertensive heart disease (fig. 2, section 4). The epidemiological method could be crucial in testing the neurogenic hypothesis of essential hypertension, as presently stated by Russian investigators.[9]

In social medicine, the problem is to relate inheritance and environment, and figure 4f is a very primitive attempt to do so.[39] Busmen in their fifties, with a parent dying at 40 to 64 years, have more hypertension than busmen whose parents lived to old age (inheritance mainly?). Drivers have higher casual pressures than conductors (environment mainly?). Comparing drivers with a parent prematurely dead, and conductors whose parents lived to 75, reveals indeed a contrast (fig. 4f). The drivers in this figure, it may be postulated, have two unfavourable features: their family history and their job. The conductors seem to have two favourable features.

Stamler's figures on obesity (fig. 4g) are for prevalence at the start of his study, and average annual incidence rates for the four years subsequent to it.[49]

Figure 4h, from Dahl,[11] is a token of the salt story; at present the epidemiological evidence, in particular from the West Indies, is contradictory.[9]

Figure 4i returns to sex and illustrates from actuarial data[6] (using life table methods) how females, who have more hypertension, cope better with it than males. The figure indicates what, on the average, individual experience may be expected.

Figure 4j, alas, is missing. The author has been unable to discover even limited data on something he wished to include, namely, information about the frequency of secondary cases of hypertension in the population during middle age compared with cases having no evident cause. It is an urgent responsibility of epidemiology to attempt to provide representative data on this question, beginning perhaps with necropsy surveys.

As clinician and laboratory worker, Wilson[54] looks for crucial contributions from epidemiology to these problems: Is essential hypertension a specific disease (qualitative);[43] or merely the tail end of the normal distribution of blood pressure in the population (quantitative)?[42] Is inheritance multifactorial, or by a single gene or a small number of genes? Is a rise of pressure in middle age physiological, or does it occur frequently in only a minority of individuals suffering from a specific disease? What are the relations between the differing levels of pressure found in population groups and their mode of life?

IMPROVEMENT OF EPIDEMIOLOGY

In field studies of blood pressure, the first casual reading is the principal measurement used. That this may often be the only practicable thing to do is scarcely virtue enough. Here is a problem urgently requiring joint work between clinicians, laboratory workers, and epidemiologists: to decide how blood pressure should be taken and recorded for population studies in this electronic age, and what other investigations can and must be made in large-scale surveys of "essential hypertension."

This questioning of the basis of most population studies of blood pressure is but one illustration of the imperative need[8, 22, 52] to improve the methods of epidemiology. Many others might be cited: streamlined electrocardiograms and automatic analysis; simple renal function tests; biochemistry of the drop of blood; classification of individual diet on a mass scale; brief psychological tests, diagnostic and predictive; "Jones criteria" for hypertension and coronary disease; semiquantitative assessment of arterial lesions; economical designs for genetic-environmental studies; measurement of personal physical activity. Help is badly needed in all of these, and more. May I close on this note?

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